The effects of cotrimoxazole or tenofovir co-administration on the pharmacokinetics of maraviroc in healthy volunteers

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AIMS

To assess the potential of cotrimoxazole and tenofovir, drugs which are inhibitors and/or substrates of renal transporters, to alter the pharmacokinetic profile of maraviroc.

METHODS

Two randomized, placebo-controlled, two-way crossover studies were conducted in healthy male and female subjects. In study 1, 16 subjects, aged 18–45 years, received maraviroc (300 mg b.i.d.) with and without cotrimoxazole (960 mg b.i.d.; 160 mg trimethoprim and 800 mg sulfamethoxazole). In study 2, 12 subjects, aged 21–45 years, received maraviroc (300 mg b.i.d.) with and without tenofovir (300 mg q.d.). For study 1, blood was collected predose and on days 1–7. In study 2, blood was collected predose, on day 1 and days 3–7. In both studies, blood was collected at intervals up to 12 h postdose on day 7. Urine was collected on day 7, 0–12 h post morning dose. Blood and urine were analysed for maraviroc using liquid chromatography/tandem mass spectrometry.

RESULTS

The geometric mean ratios for C_{max} and AUC_{12} were 119% and 111%, respectively, for maraviroc plus cotrimoxazole and 104% and 103%, respectively, for maraviroc plus tenofovir, compared with maraviroc plus placebo. Renal clearance of maraviroc plus placebo was 8.3 l h^{-1} and 8.5 l h^{-1} and was 7.8 l h^{-1} for maraviroc plus cotrimoxazole and maraviroc plus tenofovir. There were no serious or severe adverse events or any clinically significant changes in laboratory tests, blood pressure, or electrocardiograms.

CONCLUSIONS

Neither cotrimoxazole nor tenofovir caused a clinically significant effect on the pharmacokinetics of maraviroc. Maraviroc 300 mg b.i.d. was well tolerated when co-administered with either cotrimoxazole or tenofovir.

Introduction

Maraviroc is a novel, small-molecule antagonist of CCR5 [1], the chemokine coreceptor used primarily by nonsyncytia-forming, macrophage-tropic human immunodeficiency virus (HIV) isolates [2]. CCR5-tropic viruses are responsible for the majority of new HIV infections and are the predominant strain at the time of seroconversion

and during asymptomatic infection [3, 4]. CCR5 makes an attractive therapeutic target, not only because of the potential to block viral entry but also because lack of CCR5 function does not appear to have deleterious immunological consequences. Moreover, individuals who are homozygous for a null mutation on both CCR5 alleles are strongly protected against HIV infection [5].

The progression of HIV disease correlates closely with replication of the virus [6]. During short-term monotherapy in HIV-infected patients, maraviroc decreased the mean viral load by up to 1.6 log₁₀ copies ml⁻¹ after 10 days of treatment [7]. Because decreased viral load correlates with a decreased rate of disease progression, inhibition of viral entry by receptor interference appears to be an appropriate and effective antiviral therapy [8]. In clinical practice, maraviroc will be used in combination with other therapeutics, because HIV disease management requires multidrug treatment regimens to ensure virological response and prevent the development of resistant virus and concomitant conditions, such as opportunistic infections.

Cotrimoxazole and tenofovir are commonly used in the treatment of HIV and its associated conditions [9, 10]. Cotrimoxazole (a combination of sulfamethoxazole and trimethoprim) is an inhibitor of bacterial purine biosynthesis and is commonly used to treat HIV-associated *Pneumocystis jiroveci* infections [9]. The standard treatment dose of cotrimoxazole (960 mg b.i.d.) has been reported to interfere with the elimination of several drugs by various mechanisms. Competitive inhibition with trimethoprim for the human organic cation transporter (hOCT) has been implicated in the decreased renal tubular secretion of the nucleotide reverse transcriptase inhibitors (NRTI) zidovudine and lamivudine [11–13], whereas a reversible increase in serum creatinine has been reported during concomitant treatment with cyclosporin and cotrimoxazole in renal transplant patients [14]. *In vitro* data suggest that at clinical doses, sulfamethoxazole and trimethoprim selectively inhibit the cytochrome P450 (CYP) isoenzymes 2C9 and 2C8, respectively [15]. However, both sulfamethoxazole and trimethoprim lose their specificity at higher concentrations (500 µM and 100 µM, respectively) and inhibit several CYP isoforms, including CYP3A4 [15].

Tenofovir is an NRTI used in highly active antiretroviral therapy and has been associated with renal tubule defects and decreased glomerular filtration rate [16, 17]. In addition, tenofovir may be directly cytotoxic to renal tubular cells [18, 19]. Tenofovir is predominantly renally eliminated, with the involvement of both passive and active processes, suggesting the potential for competition with other drugs cleared by the same mechanisms [20]. Drug interaction studies have examined potential interactions between tenofovir and other antiretroviral agents, and, to date, only two antiretroviral drugs, atazanavir and didanosine, appear to have clinically relevant interactions requiring dose adjustments [21]. Atazanavir exposure is reduced by tenofovir [25% decrease in area under the plasma concentration–time curve (AUC)], although this effect is attenuated when ritonavir is co-administered [22]. For didanosine, concomitant administration with tenofovir increased AUC and maximum observed plasma concentration (C_{max}) by as much as 60% and 69%, respectively. Consequently, dose adjustments of didanosine have been

necessary when administered with tenofovir due to its relatively narrow therapeutic index [21, 23]. Mechanistically, tenofovir has been shown to inhibit purine nucleotide phosphorylase, which is the enzyme responsible for didanosine degradation, *in vivo* [24].

From a pharmacokinetic vantage, it is important to examine the potential for competition when concomitantly administered drugs use the same pathway for excretion or metabolism. Although maraviroc is metabolized predominantly in the liver by CYP3A4, renal clearance accounts for approximately 23% of maraviroc's total clearance [25], and involves both passive and active processes. Hence, there is a potential for interactions with drugs that compete with or inhibit these processes. Trimethoprim and tenofovir are eliminated by glomerular filtration and active tubular secretion [26, 27]. Competition for renal clearance is not of primary concern with sulfamethoxazole, which is predominantly hepatically cleared by CYP2C9 [28].

The aim of this investigation is to assess the influence of concomitant administration of cotrimoxazole or tenofovir on the pharmacokinetics of maraviroc. To assess this, two randomized, placebo-controlled, two-way crossover studies were performed in healthy subjects. In each study, maraviroc was administered in combination with either cotrimoxazole, tenofovir, or placebo, and pharmacokinetic and safety profiles were examined.

Methods

Subjects

Studies enrolled healthy male and female subjects. In study 1, subjects were 18–45 years of age, weighing between 60 and 100 kg (men) and 50 and 100 kg (women) with a body mass index (BMI) between 18 and 30 kg m⁻². In study 2, subjects were 21–45 years of age, weighing between 60 and 100 kg (men) and 50–100 kg (women) with a BMI between 18 and 28 kg m⁻². Exclusion criteria included clinical disease; significant allergies; drug hypersensitivity; investigational drug use; blood donation in the previous 2 months; positive serology for HIV, hepatitis B or hepatitis C; pregnancy or lactation; and, in study 1, sensitivity to trimethoprim or sulphonamides. Female subjects were surgically sterile, postmenopausal, or using an approved birth control method for the 3 months preceding the onset of study participation. All subjects were advised as to the risks and benefits of participation in these studies and submitted written informed consent. Studies were conducted in compliance with the ethical principles as outlined in the Declaration of Helsinki, and the study protocols were approved by an Institutional Review Board or Independent Ethics Committee at the study centre.

Study design

Study 1 was an open, randomized, placebo-controlled, two-way crossover study in 16 healthy male and female

subjects. Subjects were randomized to maraviroc (300 mg b.i.d.) + cotrimoxazole (960 mg b.i.d.: 800 mg sulfamethoxazole and 160 mg trimethoprim), then maraviroc (300 mg b.i.d.) + placebo b.i.d. or the alternative treatment sequence. Study 2 was an open, randomized, placebo-controlled, two-way crossover study enrolling 12 healthy male and female subjects who were randomized to maraviroc (300 mg b.i.d.) + tenofovir (300 mg q.d.), then maraviroc (300 mg b.i.d.) + placebo q.d. or the alternative treatment sequence. Treatment periods for both studies lasted 7 days and were separated by a minimum 7-day wash-out period (study 1) or 14-day wash-out period (study 2). Physical examinations, 12-lead electrocardiograms (ECGs), blood pressure and pulse rate assessments, drug and alcohol screening, and serology were conducted at screening, during the study treatment, and at the follow-up visit. In study 1, maraviroc was administered concomitantly with cotrimoxazole or placebo. In study 2, the morning dose of maraviroc was administered 1 h prior to breakfast. Tenofovir or placebo q.d. were administered within 30 min of breakfast (i.e. 1.5 h post morning maraviroc dose). In both studies, the morning maraviroc dose was taken under fasting conditions. Breakfast (study 2 only), lunch, dinner, and snack were served approximately 1, 4, 9 and 13 h post morning dose. Subjects in study 1 resided in the study centre for days 1–3. The evening doses on days 3, 4 and 5 were administered at home, but subjects returned to the study centre for the morning doses on days 4, 5 and 6. Subjects were re-admitted to the study centre on the evening of day 6, where they remained until 12 h postdose on day 7. In study 2, subjects were resident in the study centre throughout the dosing period.

Pharmacokinetic sampling and analysis

Blood samples were collected in nonbeaded heparinized tubes predose on days 1–7 for study 1 and on days 1 and 3–7 for study 2, and at intervals up to 12 h postdose on day 7 for both studies. Plasma was collected by centrifugation and stored for analysis.

Urine was collected in both studies on day 7 of each study period up to 12 h post morning maraviroc dose. Samples were prepared using solid-phase extraction (plasma) or protein precipitation (urine) and assayed for maraviroc using liquid chromatography and tandem mass spectrometry (Maxxam Analytics Inc., Mississauga, ON, Canada). For plasma, the overall imprecision values for the analysis of plasma quality control samples were 4.8%, 7.6% and 4.0% for maraviroc at 1, 90 and 180 ng ml⁻¹, respectively, for study 1, and 8.8%, 7.5% and 4.4% at 1.5, 150 and 400 ng ml⁻¹, respectively, for study 2. The mean inaccuracy of the assay ranged from –3.3% to 6.3%, with a calibration range of 0.5–200 ng ml⁻¹ for study 1, and –3.7% to 6.0% with a calibration range of 0.5–500 ng ml⁻¹ for study 2. For urine, the overall imprecision values were 4.4%, 3.1% and 3.3% at 15, 300 and

900 ng ml⁻¹, respectively, for study 1 and 3.1%, 3.8% and 1.5% at 15, 1500 and 3750 ng ml⁻¹, respectively, for study 2. The inaccuracy ranged from –3.7% to 6.0% with a calibration range of 5.0–1000 ng ml⁻¹ for study 1, and –4.5% to 8.0% with a calibration range of 5.0–5000 ng ml⁻¹ for study 2.

Safety

Information on adverse events (AEs) was collected throughout the study. AEs were considered potentially related to study medication for 7 days after the final dose of maraviroc. All subjects underwent a urine drug screen to test for drug abuse at screening and at specified times during the studies. Subjects with a positive result did not enter into or continue in the studies. Physical examinations, supine and standing blood pressure/pulse rate measurements, 12-lead ECGs, and laboratory safety tests were conducted at appropriate intervals throughout each study.

Statistics

For study 1, it was estimated that a sample size of 12 subjects would provide 90% confidence intervals (CIs) of ± 0.322 and ± 0.487 on the natural log scale for the AUC from 0 to 12 h (AUC₁₂) and C_{max}, respectively, with 80% coverage probability. Assuming no change in AUC₁₂ and C_{max}, it was estimated that the 90% CI for study 1 would be (76.6%, 130.5%) and (67.0% and 149.2%) for AUC₁₂ and C_{max}, respectively. Assuming a 100% increase, it was estimated that the 90% CI would be (144.9%, 276.0%) and (122.9%, 325.5%) for AUC₁₂ and C_{max}, respectively.

For study 2, it was estimated that a sample size of 12 subjects would provide 90% CIs of ± 0.216 and ± 0.372 on the natural log scale for AUC₁₂ and C_{max}, respectively, with 80% coverage probability. Assuming a 50% decrease in AUC₁₂ and C_{max}, it was estimated that the 90% CIs would be (40.3%, 62.1%) and (34.5%, 72.5%) for AUC₁₂ and C_{max}, respectively. Assuming a 200% increase in AUC₁₂ and C_{max}, it was estimated that the 90% CIs would be (242%, 372%) and (207%, 435%) for AUC₁₂ and C_{max}, respectively.

For each study, log transformed AUC₁₂ and C_{max} and untransformed time to C_{max} (T_{max}) and renal clearance (CL_R; study 1 only) were subjected to an analysis of variance allowing for variation due to sequence, subject within sequence, period, and treatment. The comparison of interest for study 1 was maraviroc and cotrimoxazole (day 7) vs. maraviroc and placebo (day 7), and for study 2, maraviroc and tenofovir (day 7) vs. maraviroc and placebo (day 7). Differences between adjusted treatment means, associated standard errors, and 90% CIs for the differences were presented on the log scale for AUC₁₂ and C_{max} and the nominal scale for T_{max} and CL_R. Log-transformed data were back-transformed to provide the ratio between the geometric means and the associated 90% CI.

Table 1

Mean pharmacokinetic parameters for maraviroc with and without cotrimoxazole (study 1)

Treatment	$T_{\max}^*$ (h)	$C_{\max}^\dagger$ (ng ml ⁻¹)	$AUC_{12}^\dagger$ (ng h ml ⁻¹)	CL_R^* (l h ⁻¹)
Maraviroc + cotrimoxazole (n = 15)	3.08 (0.76)	849 (30.7%)	3388 (22.8%)	7.81 (2.56)
Maraviroc + placebo (n = 13)	2.77 (1.70)	705 (38.7%)	3061 (20.6%)	8.34 (1.76)
Ratio (%) or difference‡	0.25	119	111	-0.59
90% CI§	-0.82, 1.32	104, 137	101, 121	-1.49, 0.31

*Unadjusted arithmetic means (SD). †Unadjusted geometric means (% coefficient of variation). ‡Ratio of adjusted means for AUC_{12} and $C_{\max}$. §Differences between adjusted means for $T_{\max}$ and CL_R .

Table 2

Mean pharmacokinetic parameters for maraviroc with and without tenofovir (study 2)

Treatment	$T_{\max}^*$ (h)	$C_{\max}^\dagger$ (ng ml ⁻¹)	$AUC_{12}^\dagger$ (ng h ml ⁻¹)	CL_R^* (l h ⁻¹)
Maraviroc + tenofovir (n = 12)	2.00 (0.00)	1245 (27.6%)	3613 (28.7%)	7.81 (1.68)
Maraviroc + Placebo (n = 11)	1.86 (0.45)	1214 (39.2%)	3536 (30.7%)	8.50 (1.38)
Ratio (%) or difference‡	0.13	104	103	ND
90% CI§	-0.13, 0.38	90, 119	98, 109	ND

*Unadjusted arithmetic means (SD). †Unadjusted geometric means (%CV). ‡Ratio of adjusted means for AUC_{12} and $C_{\max}$. §Difference between adjusted means for $T_{\max}$. ND, not determined.

Results

Subjects

Study 1 enrolled 16 subjects, mean age 24 years (range 19–43 years), with equal numbers of men and women. There were nine White subjects, six Black subjects and one Hispanic subject. The mean height and weight for the cohort were 169 cm and 73 kg, respectively. All subjects received at least one treatment regimen, and 12 of those subjects received both regimens. Of the four participants who withdrew from the study, three discontinued during maraviroc + cotrimoxazole treatment. One had an AE that was considered related to the drug (emesis), one had an AE not related to the drug, and one was no longer willing to participate. One subject discontinued the study during treatment with maraviroc + placebo due to an AE unrelated to the drug.

Study 2 enrolled 10 male and two female Asian subjects, mean age 32 years (range 22–44 years). The mean height and weight were 170 cm and 69 kg, respectively. One subject defaulted from the study during treatment with maraviroc + placebo, and withdrawal was considered unrelated to the drug.

Pharmacokinetic evaluation: effect of cotrimoxazole and tenofovir on maraviroc

The geometric mean ratios for $C_{\max}$ and AUC_{12} were 119% and 111%, respectively, for maraviroc plus cotrimoxazole

and 104% and 103%, respectively, for maraviroc plus tenofovir, compared with maraviroc plus placebo (Tables 1 and 2). Maraviroc (300 mg b.i.d.) reached steady-state levels by day 4, as defined by visual assessment of trough concentrations (data not shown).

Mean plasma concentrations vs. time profiles collected on day 7 (at steady state) for maraviroc with and without cotrimoxazole and tenofovir are shown in Figures 1 and 2.

The mean CL_R was 8.3 l h⁻¹ and 8.5 l h⁻¹ for maraviroc + placebo. Mean CL_R was 7.8 l h⁻¹ for maraviroc + cotrimoxazole and maraviroc + tenofovir. Formal statistical comparisons were only conducted in study 1, in which the difference in CL_R between treatment groups was -0.59 l h⁻¹ with the 90% CI for the difference spanning zero (-1.49, 0.306).

Safety/tolerability

Co-administration of cotrimoxazole or tenofovir with maraviroc was well tolerated in study subjects and did not result in any serious or severe AEs. In study 1, the most common treatment-related AEs were headache, nausea, abdominal pain, and vomiting, all of which occurred more frequently in the presence of cotrimoxazole, which is known to be associated with gastrointestinal AEs [29]. In study 2, the most common treatment-related AEs were menstrual disorder (tenofovir phase only) and dizziness. There were no clinically significant changes in laboratory tests, blood pressure or ECGs in either study.

Figure 1

Mean maraviroc plasma concentration–time profiles for maraviroc with and without cotrimoxazole (study 1, day 7). Maraviroc 300 mg BID + cotrimoxazole 960 mg BID (▲); Maraviroc 300 mg BID + placebo (■)

Figure 2

Mean maraviroc plasma concentration–time profiles for maraviroc with and without tenofovir (study 2, day 7). Maraviroc 300 mg BID + tenofovir 300 mg QD (▲); Maraviroc 300 mg BID + placebo (■)

Discussion

Cotrimoxazole and tenofovir are commonly used in HIV treatment regimens in combination with other medications. Both drugs have components which are excreted predominantly by the kidney and involve active processes, establishing the potential for drug–drug interactions with other agents with similar clearance mechanisms. Although maraviroc is predominantly metabolized in the liver, a proportion (23%) is cleared renally, leading to the possibility that the pharmacokinetics of maraviroc may be altered by co-administration with drugs that affect renal clearance.

Cotrimoxazole and tenofovir have been shown to decrease the rate of renal elimination of some antiretrovi-

ral drugs. Trimethoprim decreases the renal elimination of some co-administered drugs through competition for the hOCT, proteins which are responsible for the secretion of charged moieties, including many drugs, across the basolateral membrane of proximal tubular cells and into kidney tubules for excretion [26, 30]. Competition for transporters has been implicated in the reduced renal clearance of the NRTI zidovudine when administered with trimethoprim. Both drugs are secreted into kidney proximal tubules by means of the hOCT [11, 26], and when administered with cotrimoxazole in HIV-infected patients, the renal clearance of zidovudine is reduced by 58% [11, 26]. Cotrimoxazole also reduced the renal clearance of the NRTI lamivudine in HIV-infected patients by 35%, and competition for the hOCT has been proposed as the mechanism [12, 13].

Tenofovir is eliminated through active tubular secretion, and competition for transport into renal proximal tubules via human organic anion transporter 1 and 3 has been reported between tenofovir and the protease inhibitors lopinavir and ritonavir [27, 31–33]. Tenofovir may also directly affect renal function, leading to a decrease in glomerular filtration rate [16, 17, 33]. Tenofovir has been shown to alter the systemic exposure of atazanavir through a mechanism that has not been defined, but may include the induction of P-glycoprotein [34].

Although cotrimoxazole and tenofovir have been shown to alter the exposure of other drugs, neither drug produced clinically relevant changes in the systemic exposure of maraviroc.

Conclusions

Co-administration with either cotrimoxazole or tenofovir does not lead to a clinically relevant effect on the pharmacokinetics of maraviroc. Maraviroc 300 mg b.i.d. was well tolerated when co-administered with cotrimoxazole and tenofovir.

Competing interests

S.A., D.R., L.W., C.R. and G.M. were employed by Pfizer Ltd at the time of this research.

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